

# THE ROLE OF CT COLONOGRAPHY IN COLORECTAL CANCER SCREENING PERSONAL EXPERIENCE AND REVIEW OF THE LITERATURE

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## BACKGROUND

The purpose of this presentation is to provide a timely update on expanding role of Computed Tomography Colonoscopy (CTC) for colorectal cancer (CRC) screening.

Colorectal cancer mortality can be reduced through early diagnosis of advanced neoplasia, which includes both colorectal cancer itself, as well as benign but histologically advanced adenomas that are at increased risk for progression and malignancy. The goal of screening is to detect cancer at an early, curable stage and to detect and remove clinically significant adenomas.

Recently published guideline recommendation from The American Cancer Society, in conjunction with the major gastroenterology and radiology societies propose prevention of CRC through detection of advanced adenomas with complete structural examination, either with optical colonoscopy or computed tomography. While colonoscopy is currently the preferred test for CRC screening, the invasive and time consuming characteristics of the test are often cited as the reason for noncompliance with screening. CT colonoscopy is less invasive test with high accuracy, excellent clinical performance, safety profile, and cost effectiveness. CTC has been integrated into established screening programs as a replacement for barium enema in the case of incomplete colonoscopy. In addition to the intended colorectal evaluation, CTC also provides assessment of extracolonic structures, including abdomen, pelvis and lung bases.

The main potential drawback of the CTC screening is the exposure to ionizing radiation. Low-dose protocols are now routinely implemented, delivering a dose comparable or slightly superior to the annual radiation exposure of any individual.

## INTRODUCTION

Colorectal cancer (CRC) is a major cause of morbidity and mortality in Western societies.[1] According to the widely accepted adenoma-carcinoma sequence, most cancers develop from a small subset of benign adenomatous polyps over a long period of time. CRC largely can be prevented

by the detection and removal of clinically important polyps, and survival is significantly better when the disease is diagnosed when still is localized. The goal of cancer screening is to reduce mortality through a reduction in incidence of advanced disease [1,2]. This means detection of early stage adenocarcinomas and the detection and removal of adenomatous polyps. Multiple screening tests already exist with varying capability, cost, and invasiveness. They are divided into two categories: stool tests and structural exams [3]. These tests may be used alone or in combination to improve sensitivity or, to ensure a complete examination of the colon if the initial test cannot be completed. None of the standard tests is therefore optimal in terms of safety, cost, or performance.

Computed tomographic colonography (CTC) is a relatively new, noninvasive technique for large bowel imaging that has the ability to detect colorectal neoplasia [6]. This diagnostic test has recently been advocated by multiple American Professional societies as an effective alternative for CRC screening [1,2]. The potential advantages of CTC include rapid image acquisition and processing, non-invasiveness, and decreased procedural risk of perforation, bleeding, and sedation complications. This may serve to improve the low rates of colorectal cancer screening that are currently observed in our society [3]. As with any new screening test, CTC has come under much scrutiny when considered in the broader context of recommended CRC screening tests. Specifically, issues related to test accuracy, programmatic feasibility and compliance, the cost and management of intracolonic and extracolonic findings continue to generate debate in the medical communities.

CTC has been integrated into established screening programs as a replacement for barium enema (BE) in the case of incomplete conventional colonoscopy (CC)[4]. Numerous evidence exists in the literature showing a clear superiority of CTC over BE in the detection of CRC and polyps [5,6,7]. Performing CTC in patients with a positive Fecal Occult Blood Test (FOBT) would not be an efficient triage technique in terms of cost effectiveness, due to the high prevalence of clinically relevant lesions [8,9]. In March 2008 the American Cancer Society (ACS), the U.S.Multy-Society Task Force on Colorectal Cancer and the American College of Radiology (ACR) released consensus guidelines on CRC screening for average-risk individuals. These guidelines distinguished diagnostic tests into

two groups- those able to detect CRC and potentially reducing mortality (FOBT; Fecal Immunochemical Stool Testing; FIT; and stool DNA testing), and those able to detect both polyps and cancer and potentially reducing both the incidence of and the mortality from CRC. The latter group of tests includes conventional colonoscopy, sigmoidoscopy, BE and for the first time- also CTC. They recommended CTC to be performed in average risk individuals as screening test every 5 years, starting at age of 50 [2]. Unfortunately, the position of the US Preventive Services Task Force (USPSTF) differs significantly. They considered the evidence insufficient to be assessed the benefits and harms of CT colonography. They focused on unknown impact of extracolonic findings and radiation exposure, the poor data on cost and cost effectiveness, and the still unsolved problem of ideal bowel preparation [10]. The American College of Gastroenterology consider CTC a second line screening test for patients, unwilling or unable to undergo CC and for those in whom CC was incomplete/[11].

### EFFICACY

The issue of diagnostic accuracy of CTC for detection of CRC and polyps has been debated a long time, because of the conflicting results in some of the papers published in the literature [12-14]. This has been recently confirmed by a meta-analysis showing that "CTC is highly specific for the detection of colorectal polyps and tumors" and that "studies reported high sensitivities, but the results of the studies were highly heterogeneous, while the studied variables explained only part of this discrepancy"[15].

To elucidate these discrepancies three important studies have been created:

- The American College of Radiology Imaging Network (ACRIN) trail, which is large, multicenter study, testing the performance of CTC in comparison with CC in asymptomatic subjects at average risk [16].
- The Italian Multicenter Polyps Accuracy CTC Study (IMPACT), which observe a mixed population of asymptomatic subjects at risk higher than average and patients with positive FOBT [17].
- The Special Interest Group in Gastrointestinal and Abdominal Radiology (SIGGAR) trail, conducted on symptomatic patients with the aim to detect CRC [18].

The ACRIN trail tried to minimize the variables possibly affecting CTC performance. Only 16 row scanners were included, preparation for the patients was standardized with cathartic agent for bowel cleaning and oral contrast for fecal tagging. Only trained radiologists were engaged in image interpretation.

Both the ACRIN and IMPACT trails reported per-patient sensitivity of 90% for polyps larger than 10 mm and 78-84% for polyps larger than 6 mm. Per patient specificity was extremely high as well, over 85% independently of lesion size. The major drawback of ACRIN was represented by the poor positive predictive value (PPV) (23% for polyp's  $\geq 10$ mm). A definitely better PPV was documented

in the IMPACT trail (62% for lesions larger than 6 mm) as well as in studies obtained in high experienced centers. However the negative predictive value in both the ACRIN and the IMPACT trails was rather high, according 100%. This is very important in order to reassure negative patients about the significance of the examination.

The results from CIGGAR trail are still under data analysis. Excellent results were also obtained in the Munich Colorectal Cancer prevention Trail [19], which included 307 asymptomatic adults that were scanned with CTC and subsequently underwent same-day optical colonoscopy. The results show CTC sensitivity for the detection of clinically relevant polyps  $\geq 6$  mm of 84% (84/100 polyps), while optical colonoscopy detected 92% of these lesions. For large lesions  $\geq 10$  mm, CTC achieved 87.5% sensitivity, while all of these lesions were detected by colonoscopy. Importantly, CTC specificity for these size groups was 95.9% and 98.6%, respectively.

It is important to mention the screening project offered by the University of Wisconsin [20]. 3000 subjects in two different, nonrandomized groups underwent CTC and CC. The detection rate for advanced adenoma was 3.2% for CTC and 3.4% for CC (difference not statistically significant). The main advantage was the reduction in the number of polypectomies in the CTC group without any complication as opposed to seven perforations which occurred in CC group.

Despite the good results there are still some open issues under debate: the management of intermediate (6-9mm) lesions, the detection rate for non-polypoid, flat lesions and the impact of the extracolonic findings.

Lesion size is widely accepted as undoubtedly the most important determinant of clinical significance. Larger lesions are more often neoplastic; more frequently show advanced histology; and, of course, represent the vast majority of life-threatening cancers [21]. Large adenomas ( $\geq 10$  mm) compose about 90-95% of all advanced neoplasia [26]. Diminutive lesions (polyps 5 mm in size) detected at CTC are usually benign and do not appear to be a compelling reason for colonoscopy and polypectomy. As a general rule, approximately one third of diminutive lesions are adenomatous and two thirds are nonadenomatous, predominately consisting of nonneoplastic mucosal tags and hyperplastic polyps [22]. Above the 6-mm size threshold, the ratio of adenomatous to nonadenomatous polyps reverses, with neoplastic lesions representing approximately two thirds of nondiminutive lesions. A real controversy exists regarding the clinical management of small (6-9mm) polyps detected at CTC. To objectively analyze this issue we have to focus on the behavior and natural history of small colorectal polyps in a screening population.

Because most polyps detected at primary optical colonoscopy screening are generally removed, polyp histology according to lesion size has been well established. But the histology of resected polyps does not provide precise information regarding clinical behavior or significance. Therefore, polyp histology alone does not reliably predict the growth rate and future risk if the polyp had been

left in place. Furthermore, it is very important to ascertain whether the data are derived from asymptomatic screening populations or symptomatic high-risk cohorts because the rates of clinically important histology will greatly differ between these two groups.

The management of CTC findings is an important part of a CTC screening program. A rational evidence-based screening algorithms and surveillance guidelines based on polyp size is an important challenge. Most experts would agree that large polyps ( $\geq 10$  mm) detected at CTC screening will generally warrant polypectomy, whereas immediate colonoscopy is not necessary for isolated diminutive polyps ( $\leq 5$  mm). At this time, there is consensus that all patients with one or more polyps  $> 10$  mm or 3 or more polyps  $> 6$  mm detected at CT colonography should be referred for colonoscopy [21]. The management of patients with fewer polyps ( $< 3$ ) in which the largest polyp is 6 to 9 mm remains controversial. Based on expert consensus and until further evidence is available to provide additional guidance, a reasonable approach at this time for patients with 6 to 9 mm polyps identified on CTC is to recommend therapeutic colonoscopy. Patients who decline referral to colonoscopy or who are not good candidates for colonoscopy should be offered surveillance with CTC.

At least one colorectal polyp may harbor in 35-50% of adults over the age of 50 years [16,22,23]. The prevalence range for polyps 6 mm and larger is 13-16%. The overall prevalence of large polyps in this population is 5-6%, whereas about 8% have a polyp in the 6 - to 9-mm range [24].

Polyp's morphology is another important feature. Polyps are generally divided into three major morphologic categories: sessile, pedunculated, and flat. Sessile polyps have a broad base of attachment, whereas pedunculated polyps have a defined head and stalk that connects the lesion to the adjacent colonic surface.

The term "polypoid lesions" refers to both sessile and pedunculated polyps.

These polyps account for the vast majority of cases, including most advanced adenomas and cancers [25]. Flat lesions represent a subset of sessile polyps with elevation above the surrounding mucosal surface of 3 mm or less. The term "carpet lesion" refers to laterally or superficially spreading tumor, that tend to be quite large in cross-sectional area but not bulky [27].

Because flat lesions are generally less conspicuous than polypoid lesions, they can be more challenging to detect initially at both CTC and optical colonoscopy. Endoscopic detection of nonpolypoid lesions may be increased by the use of advanced endoscopic techniques, such as chromoendoscopy and narrow-band imaging. A potential disadvantage of CTC would be the possible impaired ability to detect non-polypoid, flat lesions. Unfortunately, at the moment only few and conflicting data about the sensitivity of CTC for flat lesions are available. At the beginning disappointing results were published, because of technical limitations as well as readers' experience [28]. More recently, better results were reported, with sensitivity in the range of 80% - 90% for flat adenocarcinomas [23,30].

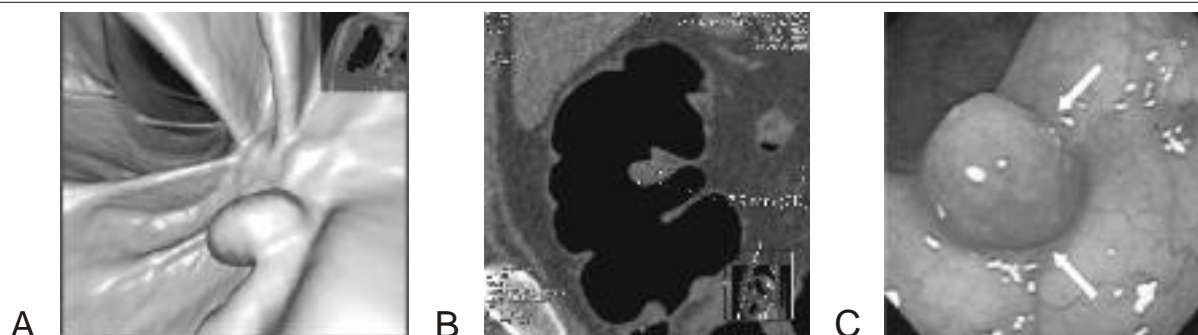


Fig. 1. Small (7.9 mm) sessile right colonic lesion: A- CT colonography-ennoluminal view; B- CT colonography-2D image-oblique reconstruction; C- conventional colonoscopy

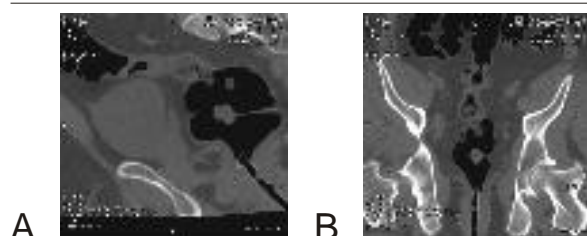


Fig. 2. Pedunculated polypoid lesion on left lateral rectal wall, presented on CT Colonography - 2 D reconstructed images: A - sagittal reconstruction; B - curved reconstruction



Fig. 3. A 52 year old man with 25/2 mm (width/height) flat adenocarcinoma on the sigma wall. A. 2D axial image of CT colonography shows slightly elevated carpet lesion; B. CC demonstrated profile view of plaque like, slightly elevated lesion in sigma;



These results seem to be confirmed by a recent retrospective analysis of the data from the ACRIN trial showing a sensitivity of 89% for flat adenomas  $\geq 6$  mm (at the prospective analysis, sensitivity was 68%) [16].

### **COMPLIANCE (ADHESION TO A SCREENING PROGRAM)**

Adhesion of healthy individuals to a screening program is a very complex and important issue [29]. CC, accepted as the most effective screening method, suffers from a very low participation rate [35]. Implication of the invited population affects directly the efficiency of the screening program, because it is a function of both test sensitivity and user rate. Therefore, an increase of the screening uptake will increase the overall screening efficiency. Acceptance of a screening study by a population is multi-functional. Many physical and psychological barriers to colorectal cancer screening have been described. Surveys have reported patients' reluctance to undergo CRC screening because of time commitment for the CC, use of colon cathartics, sedation requirements, prior painful experience and even embarrassment [36]. Bowel preparation is often perceived as the most unpleasant part of the examination [32]. Sedation during CC is an advantage, which is applied to increase the adhesion rate to a screening program [31].

CTC as a screening tool has the potential to have wider public acceptance compared to CC. CTC is relatively fast without the need for sedation and has emerged as a potentially more comfortable alternative for patients undergoing full structural screening of the colorectum. Patients have described the post procedure discomfort less for CTC than CC. The advantage of CTC is the possibility to use of a gentler preparation or unprepared (laxative-free) examination [33]. The pain related to colon distention by air may be minimized by the use of carbon dioxide delivered by an electronic pump. The use of carbon dioxide is also associated with a faster absorption, making the patient more comfortable immediately after the examination [34].

Several studies have shown that patients' acceptance of CTC is greater than CC or double contrast barium enema and could be able to increase screening uptake [39].

A subset of patients, including the elderly, those with cardiovascular disease, bleeding diathesis and a history of failed colonoscopies, are better suited to undergo CTC for CRC screening compared to colonoscopy or DCBE.

### **SAFETY**

CTC is safe test, definitely safer than CC. The results of different surveys show a perforation rate associated with CTC ranging between 0.06% and 0.08% [35,37], compared with 0.1%-0.2% for diagnostic colonoscopy [38]. It should also be noted that comparison between CTC and CC is very difficult, with the risk of overestimating the clinically significant perforations at CTC, because of the much higher sensitivity of CT in the detection of even tiny air bubbles. These small perforations during CTC usually are treated conservatively, without surgical intervention. The use of rigid catheter for bowel distention and manual insufflations

of air are the main reasons for complications during CTC procedure. Now rigid catheters are displaced by rubber devices and the distention of the colon is achieved by the use of electronic pump, delivering carbon dioxide, able to control pressure and volume.

The main potential drawback of screening with CTC is the exposure to ionizing radiation and the consequent theoretical risk of inducing cancer. The dose delivery with CTC is usually higher compared with a standard abdominal CT study due to routine use of prone and supine scans. Radiation exposure has also substantially increased over the past few years due to consequent increase of tube current setting in order to reduce image noise. This represents a crucial issue for proposing CTC as a screening method for colonic polyp in healthy subjects. Low or ultra low dose MDCT protocols together with new automatic dose modulation software may help in solving this problem [40].

### **ADDITIONAL FINDINGS**

A unique added dimension of CTC screening compared with endoscopy is the ability to evaluate extracolonic structures of the abdomen and pelvis. Abnormal lesions in other abdominal organs, such as the liver, kidneys, adrenal glands, and abdominal aorta, may be visualized simultaneously with the colon. In a previous study, Hara et al. [41] reported that 11% of patients undergoing CT colonography had incidental extracolonic findings that were classified as highly important. Detection of incidental extracolonic findings has many possible advantages, such as early detection of malignant disease or of an unruptured abdominal aortic aneurism. Early treatment can improve a patient prognosis and decrease cost owing to less complicated surgical procedures and shorter hospital stay. On the other hand, extracolonic findings leading to further work up may cause unnecessary patient anxiety, entailing higher cost and superfluous exposure to radiation. Detection and evaluation of extracolonic findings therefore balances between potential benefits and potential harm.

### **CONCLUSION**

Computed tomographic (CT) colonography is a rapidly evolving technique for the detection of colorectal polyps and cancers. Its sensitivity is better than that of double-contrast barium enema examination for detection of colonic cancer and polyps. CTC has been recommended as alternative to double-contrast barium enema examination in patients with incomplete colonoscopy. CT colonography has accuracy similar to that of conventional colonoscopy both in high-risk groups and in a low-prevalence screening population. It has the potential for selectively and noninvasively identifies those patients who would clearly benefit from therapeutic colonoscopy. Although concerns about performance consistency, technical variability, and clinical implementation need to be resolved before CT colonography can be advocated for widespread colorectal cancer screening.

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